
Manual of Standard Operating Procedures and Policies

Regulatory - License Applications

Determining When Prelicense / Preapproval Inspections are Necessary

SOPP 8410

Version #4

Date: December 4, 2001

1. Purpose

The purpose of this document is to describe the policies and procedures for determining when pre-license or pre-approval inspections are necessary for completing the review process or evaluating the compliance status of establishments that perform manufacturing steps included in Biologics License Applications (BLA) or supplements submitted to CBER.

2. Definitions

Pre-license inspection

An inspection of an establishment that has not been licensed or approved by CBER for the product under review. This includes establishments that already have approved products regulated by CDER or CDRH or an establishment that has one or more biologics license(s) or approvals for other products.

Pre-approval inspection

An inspection of an establishment that performs manufacturing steps in an approved BLA and for which the applicant has submitted a supplement for a significant manufacturing change or other change that ordinarily requires on-site review of the change.

3. Background

Section 351 of the Public Health Service Act and section 704 of the Federal Food, Drug and Cosmetic Act provide the regulatory authority to conduct inspections at any establishment where biological products are manufactured. Under 21 CFR 601.20, a biologics license shall not be issued except upon a determination that the product and establishment comply with the applicable regulations. Under the reauthorization of Prescription Drug User Fees (PDUFA2) in the Food and Drug Administration Modernization Act of 1997, an inspection, if needed, is considered to be part of the complete review of an application.

Compliance Program 7346.832 ("Pre-approval Inspections/Investigations") provides a strategy for assigning pre-approval inspections to the Office of Regulatory Affairs (ORA) by the Center for Drug Evaluation and Research (CDER) and describes those circumstances in which an inspection is necessary prior to approving an application; in other circumstances, the pre-approval inspection is optional. In a continued effort to harmonize with CDER, this SOP is being developed for CBER pre-license and pre-approval inspections.

It has been CBER's policy to conduct pre-license or pre-approval inspections for all new BLAs and significant manufacturing or establishment change supplements. As a result of recent regulatory changes, including the revision of the definition of manufacturer (61 FR 24227, May 14, 1996), CBER has noted an increase in contract manufacturing arrangements, which in turn has increased the number of inspections that need to be conducted. This has meant some duplication of FDA's inspection efforts, as CBER and ORA inspect some establishments several times per year, even when the establishments have a good compliance history. This is not only burdensome to the industry and the agency, but the additional inspections have not provided a significant degree of added assurance that the product and establishment are in compliance with the applicable regulations and standards. This is the case because systems and facilities may have already been comprehensively evaluated in previous inspections.

Recently, review time frames have decreased for some applications and supplements. Some submissions require a priority review because of the serious or life-threatening nature of the condition being treated by the product. Other review management changes have modified the review process to clarify that inspections are part of the complete review of a BLA. Also, CBER now relies on inspections to obtain information previously submitted in the application, thus requiring greater coordination and efficiency in planning and conducting inspections. However, some BLAs and supplements include manufacturing establishments that use production areas common to other licensed products, so conducting a pre-license or pre-approval inspection prior to approval of every BLA or supplement may not be necessary.

4. Policy

CBER's policy is to ensure that manufacturing establishments and processes meet the appropriate requirements and comply with the regulations through inspections and other mechanisms. Because of the commitment to PDUFA II timeframes, CBER will make the best use of its resources for review and inspection. CBER will determine if a pre-license or pre-approval inspection is necessary by assessing whether an inspection provides any additional benefit towards protecting the public health and assuring compliance with applicable requirements. There may be circumstances when pre-license or pre-approval inspections are not the best use of CBER resources; therefore, CBER will rely on information gathered in other inspections to evaluate the establishments.

It is CBER's policy that a pre-license or pre-approval inspection will generally be necessary for a BLA or supplement if any of the following criteria are met:

- The manufacturer does not hold an active U. S. license, or, in the case of a contract manufacturer, is not approved for use in manufacturing a licensed product.
- FDA has not inspected the establishment in the last 2 years.
- The previous inspection revealed significant GMP deficiencies in areas related to the processes in the submission (similar processes) or systemic problems, such as QC/QA oversight.
- The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.
- The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment. Points to be considered:
 - Do differences in the process (e.g., different types of columns) or particulars (e.g., different production cell lines) require an on-site determination of GMP compliance?
 - Are the analytical methods accurate/sensitive enough to detect problems?
 - Are different equipment or processes being used?

Even if the above criteria would otherwise call for an inspection, the inspection may be waived if the establishment only performs ancillary testing (testing not impacting release of the drug substance or drug product) for the submission under consideration. An inspection should not be waived on the basis of requesting the applicant to submit additional information that would not normally be submitted to a BLA or supplement.

Most supplements will not need a pre-approval inspection. Prior-approval supplements (PAS) describe changes

that have a substantial potential to have an adverse effect on the product, so PAS will usually be the only type of supplements to contain issues significant enough to warrant an inspection. Examples of PAS that may require a pre-approval inspection as part of the approval process:

- A new manufacturing site/suite/building/room
- A significant change in the manufacturing process
- Change of a contract manufacturing location for a processing step that has a substantial potential to have an adverse effect on the product
- For establishments that manufacture whole blood and blood components, a supplement to add a new product, process (e.g., irradiation), or program (e.g., red blood cell immunization) to the approved license
- Supplements submitted under Pilot Program initiatives.

5. Procedures

Applications

- At the application filing meeting, the review committee should determine if the establishment(s) used in the manufacture of the product which is the subject of the BLA meet any of the criteria listed in the Policy section. If none of these criteria apply, the committee may recommend that the inspection(s) be waived (Appendix 1.). If the BLA includes multiple manufacturing establishments, the committee may recommend the inspection be waived for any or all of the establishments; however, each establishment must be assessed separately against the above criteria. The meeting minutes should include the opinion of the committee regarding the need for inspection.
- If the review committee determines an inspection will not provide any additional public health benefit, the review committee should send a memo with a recommendation that the inspection be waived to the Director of the division with product responsibility and the Director, Division of Manufacturing and Product Quality (DMPQ), OCBQ. Both of these people must concur in the decision to waive an inspection, or the inspection should be scheduled according to established procedures. If the committee includes a DMPQ reviewer, the DMPQ reviewer is responsible for drafting the memo. If the committee does not include a DMPQ reviewer, the committee chair or RPM is responsible for drafting the memo. A copy of the memo should be sent to the Director of the applications division in the product review office and the Branch Chief of the Program Inspection Branch, Division of Inspections and Surveillance, OCBQ, for their information.
- If an inspection is waived, documentation of the decision to waive the inspection and the basis for waiving the inspection should be included in the license application file.
- The decision and documentation should occur as soon as possible after the filing meeting, generally within 30 days. This procedure may not apply to certain blood and blood component applications as outlined in Office of Blood Research and Review SOPPs.
- If the application is deficient in some material sense such that the firm would have to put forth significant effort to address the deficiency, e.g., an additional clinical study or substantial manufacturing changes or the firm would need at least a year or more to correct deficiencies, the review committee may decide that the inspection should be postponed until the applicant has submitted information to address the deficiency. The Director, DMPQ, and the Director, product division, should concur in the decision to postpone the inspection. In this case, a complete response letter may be issued without an inspection having been performed. The complete response letter should inform the applicant that because of the length of time anticipated to correct the deficiencies, CBER will not perform an inspection until the applicant submits information that appears to address the deficiencies.

Applications and Supplements

- If CBER is informed by the applicant or ORA that the establishment(s) are not ready for inspection, and all other portions of the review have been completed by CBER, a complete response letter may be issued

without performing an inspection. The complete response letter should include the lack of availability of the establishment(s) for inspection as a deficiency.

- If the particulars of the submission are not adequately addressed by the criteria above, or if the review committee agrees that an inspection is not appropriate but the situation does not meet the criteria above, the RPM should schedule a meeting with the appropriate office representatives, including the product office and the Office of Compliance and Biologics Quality (OCBQ), to discuss and recommend a course of action for the Director, CBER or Deputy Director/Operations, CBER.

Supplements

At the filing meeting, the review committee should determine if the changes reported in the supplement are of a nature to require on-site review. This determination should include a consideration of the criteria above for deciding whether an inspection should be performed. If the review committee determines an inspection is necessary for one or more establishments included in the supplement, the decision should be documented in the meeting minutes and the inspection(s) should be performed prior to sending the action letter for the supplement. Documentation of the decision to waive an inspection and the basis for waiving the inspection should be included in the license application supplement file. The decision and documentation should occur as soon as possible after the filing meeting, generally within 30 days.

6. Effective Date

December 4, 2001

7. Appendix

[Appendix 1: Waiver Recommendation Memorandum](#)

8. History

Written/Revised	Approved	Approval Date	Version Number	Comment
RPS	Robert Yetter, Ph.D.	January 15, 2003	4	Revised to include OCC change in template language; also includes technical changes.
Paula McKeever, RMCC	Robert Yetter, Ph.D.	January 15, 2003	3	Addition of updated instructions and templates.
S. Sensabaugh/ G. Hicks	Rebecca Devine, Ph.D.	June 24, 1997	2	Reissued as SOPP 8002 in August 1997. No change to Guide content.
S. Ripley	Rebecca Devine, Ph.D.	December 31, 1996	1	Revisions to content pursuant to FDA Modernization Act of 1997.

Updated: December 10, 2001